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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,394	12/17/2004	Bernard Vacher	03715.0144	8214

22852 7590 05/30/2008

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EXAMINER	
O'DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
05/30/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,394	VACHER ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5 and 9-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5, 9-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-11 are pending in the current application.

2. This application is 371 of PCT/FR03/01873 filed 06/18/2003 which claims benefit to French application 02/07470 filed 06/18/2002.

Response to Arguments

3. The claim amendments and arguments have been considered and deemed to overcome the rejections of record since the instant claims are now drawn solely to the diazines and have eliminated the pyridine derivatives which were the basis of the rejection, however the examiner had overlooked the "hydrate" limitation previously and now makes a new ground of rejection. The new claims are not subject to rejoinder until the product claims are found allowable and thus stand withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-8, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making hydrates of the salts of claimed compounds. The specification does not enable any person skilled in the art of synthetic organic chemistry to make the invention commensurate in scope with these claims. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples,

d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. In the present case the important factors leading to a conclusion of undue experimentation are the absence of any working example of a formed solvate, the lack of predictability in the art, and the broad scope of the claims.

c) There is no working example of any hydrate of a salt formed, while . The claims are drawn to hydrates, yet the numerous examples presented all failed to produce a hydrate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that hydrates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that hydrates can be made, or limit the claims accordingly.

g) The state of the art is that is not predictable whether hydrates will form or what their composition will be. In the language of the physical chemist, a hydrate of an organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). West, Anthony R., "Solid State Chemistry and its Applications, Wiley, New York, 1988, pages 358 & 365. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page

365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed hydrate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. In the same paragraph on page 365 West (Solid State Chemistry) explains that it is possible to make meta-stable non-equilibrium solvates, further clouding what Applicants mean by the word hydrate. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stabile region of the solvate.

h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula I as well as the presently unknown list of solvents embraced by the term "solvate". Thus, the scope is broad.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites dependence on "certain substances", without actually explaining what the substances are. The scope of this claim is unascertainable. Certain has several meanings according to the The American Heritage Dictionary of the English Language: Fourth Edition:

1. Definite; fixed: *set aside a certain sum each week.* **2.** Sure to come or happen; inevitable: *certain success.* **3.** Established beyond doubt or question; indisputable: *What is certain is that every effect must have a cause.* **4.** Capable of being relied on; dependable: *a quick and certain remedy.* **5.** Having or showing confidence; assured. **6a.** Not specified or identified but assumed to be known: *felt that certain breeds did not make good pets.* **b.** Named but not known or previously mentioned: *a certain Ms. Johnson.* **7.** Perceptible; noticeable: *a certain charm; a certain air of mystery.* **8.** Not great; calculable: *to a certain degree; a certain delay in the schedule.* "certain" The American Heritage Dictionary of the English Language: Fourth Edition. 2000, online "http://www.bartleby.com/61/39/C0213900.html" accessed May, 20, 2008.

If meaning one or three is intended, is this meant to include all substances that have a definite structures to the exclusion of substances that have undefined or "uncertain" structures? For example would a substance like Factor S (Richard Cammack Oxford Dictionary of Biochemistry and Molecular Biology Oxford University Press: 2006, pg. 234), which has an unknown or uncertain structure be excluded? If the definition intended is 6a or 6d the substances are then "not specified or identified but assumed to be known" and do not meet the requirements of 112 2nd paragraph. Because the meaning of a claim term as understood by persons of skill in the art is often not immediately apparent, and because patentees frequently use terms idiosyncratically, the court looks to sources available to the public that show what a person of skill in the art would have understood disputed claim language to mean. Those sources include the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art. Phillips v. AWH Corp., 415 F.3d 1303, 75 USPQ2d at 1327. (Fed. Cir. 2005).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 9-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention
In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(B) The nature of the invention: This is medical invention requiring the treatment of a depression, pain and dependence on "certain substances". **(D) The level of one of ordinary skill**: One of ordinary skill is a medical doctor. **(C) The state of the prior art (E) The level of predictability in the art; (F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:** The inventor has provided no working examples of the treatment of a disease. In fact the only information provided is an assay for agonism at the 5HT1a receptor. This receptor is a GPCR with a vast number of binding sites and conformations each of which may be associated with a distinct physiological outcome. One reviewer has summarized the situation this way (Terry Kenakin and Ongun Onaran "The ligand paradox between affinity and

efficacy: can you be there and not make a difference?" *TRENDS in Pharmacological Sciences* **2002**, *23*, 275-280):

"A probabilistic model of protein conformation can be used to quantify the probability of various receptor conformations and the effect of ligand binding on those conformations. The basic idea behind the probabilistic model is that the function of a receptor protein is not assigned to particular conformations of the receptor. Instead, the function arises as a result of ligand-induced perturbation of the distribution of conformational states over the conformational space of the receptor.....**The foregoing discussion leads to the general conclusion that if a ligand binds to the receptor, it most probably will produce a bias in the conformations of the receptor ensemble** [i.e. it will change the receptor by its presence (Fig. 3)]. Therefore**, this suggests that all ligands with macro-affinity should be extensively studied for pharmacological activities other than simple G-protein activation because various physiological activities have been defined that are mediated by conformations not necessarily related only to G-protein activation**..... "

Here we have exactly this situation, namely a ligand with affinity, but limited information about its function, which as Kenakin et. al. concluded "...the discovery of macro-affinity of a ligand for a receptor should be considered only a starting point for the optimal exploitation of a drug for therapeutic utility." While it is clear that some of these compounds are agonists or partial agonists at the 5-HT1a receptor (GTP-γ-S binding), nothing else is known about them. The number of coupling partners associated with this GPCR is quite large, the interaction with these proteins and the subsequent signaling of the $5HT_{1a}$ receptor is complex, Raymond, John R "The recombinant 5-HT_{1A} receptor: G protein coupling and signalling pathways." *British Journal of Pharmacology*, **1999**, 127(8), 1751-1764.

".....The realization that the 5-HT1A receptor couples to multiple signalling pathways in cells and tissues in which it is normally expressed reflects a relatively new understanding of the potential promiscuity of receptor-G protein signalling pathways. Nevertheless, it has long been suspected that single receptor subtypes might be linked to various second messengers in a single cell system ...The recombinant 5-HT1A receptor has been shown to regulate the function of several distinct types of channels, including inwardly rectified K+ channels, high conductance anion channels, CFTR Cl7 channels, and Ca2+ channels. G protein-gated inwardly rectified K+ (GIRK) channels mediate hyperpolarizing postsynaptic potentials in the nervous system and in the heart during activation of Gi/oa-coupled receptors, including the 5-HT1A receptor....In addition to regulating channels, the 5-HT1A receptor has been shown to activate several active ion transport processes....."

The specification does not elaborate on the type of cells used in the assay, were these tranfected cells expressing recombinant receptor, or primary cells with native receptor? The difference between behavior of a compound in tissue can be quite different from the recombinant system. Regardless, the information given, namely that the compounds are agonists at the 5HT1a receptor, does not correlate with treatment. Of course all therapeutically effective compounds have affinity for their respective targets, but it is specious logic that leads one to the converse that all active compounds are therapeutically useful. Consider the fact that LSD is an agonist at the 5-HT1a receptor, see Norman, Andrew B. et. al. "[3H]Lysergic acid diethylamide (LSD): differential agonist and antagonist binding properties at 5-HT receptor subtypes in rat brain." *Neurochemistry International* **1989**, 14(4), 497-504. If the reasoning put forth by the applicant holds true then LSD should be used to treat depression, pain, and addictions to "certain substances", however I think no medical doctor would suggest that LSD be given to these patients. Just because a compound may be a an agonist this does not preclude its potential for therapeutic utility, however GPCRs are not to be viewed as G-protein switches effectively treating diseases when switched on or off. It is undue experimentation to take a compound that has the data revealed in the specification and extrapolate these results into complex diseases.

See MPEP 2164.02: CORRELATION: IN VITRO /IN VIVO

> The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between in vitro or in vivo animal model assays and a disclosed or a claimed method of use. An in vitro or in vivo animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that

> the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that in vitro data did not support in vivo applications). Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an in vitro or in vivo animal model example. A rigorous or an invariable exact correlation is not required, as stated in Cross v. Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985): [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)

There is no correlation between the assays that were conducted and the many diseases described. The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification , at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has no working examples in this unpredictable art without undue experimentation.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

/Rita J. Desai/
Primary Examiner, Art Unit 1625